Origins and consequences of antimicrobial-resistant nontyphoidal *Salmonella*: implications for the use of fluoroquinolones in food animals

Angulo F, Johnson K, Tauxe R, Cohen M

ABSTRACT

Human *Salmonella* infections are common; most infections are self-limiting, however severe disease may occur. Antimicrobial agents, while not essential for the treatment of *Salmonella* gastroenteritis, are essential for the treatment of thousands of patients each year with invasive infections. Fluoroquinolones and third-generation cephalosporins are the drugs-of-choice for invasive *Salmonella* infections in humans; alternative antimicrobial choices are limited by increasing antimicrobial resistance, limited efficacy, and less desirable pharmacodynamic properties. Antimicrobial-resistant *Salmonella* results from the use of antimicrobial agents in food animals, and these antimicrobial resistant *Salmonella* are subsequently transmitted to humans, usually through the food supply. The antimicrobial resistance patterns of isolates collected from persons with *Salmonella* infections show more resistance to antimicrobial agents used in agriculture than to, antimicrobial agents used for the treatment of *Salmonella* infections in humans. Because of the adverse health consequences in humans and animals associated with the increasing prevalence of antimicrobial-resistant *Salmonella*, there is an urgent need to emphasize non-antimicrobial infection control strategies, such as improved sanitation and hygiene, to develop guidelines for the prudent usage of antimicrobial agents, and establishment of adequate public health safeguards to minimize the development and dissemination of antimicrobial resistance and dissemination of *Salmonella* resistant to these agents.

INTRODUCTION

The discussion about adverse human health effects associated with the veterinary use of antimicrobial agents has been clouded by confusion surrounding the origins and consequences of antimicrobial-resistant nontyphoidal *Salmonella* infections in humans.[24.43] (This report pertains only to nontyphoidal *Salmonella*.) This issue needs to be revisited in the light of recent discussions concerning the public health implications of veterinary use of fluoroquinolones,[2.3] a class of antimicrobials essential for treatment of several life-threatening infections in humans.[13.44] Because of these public health concerns, the Food and Drug Administration prohibited the extra-label use of fluoroquinolones in food animals in the United States in August, 1997.[15] However, two fluoroquinolones, enrofloxacin and sarafloxacin, were approved in 1995 for use in poultry in the United States.[8] To address the human health implications of the veterinary use of fluoroquinolones, we review here the clinical significance of antimicrobial-resistant *Salmonella* infections in humans, the epidemiology of antimicrobial-resistant foodborne pathogens including *Salmonella*, the sources of *Salmonella* (including antimicrobial-resistant *Salmonella*) infections in humans, the causes and consequences of development of antimicrobial-resistant *Salmonella*, and we suggest necessary actions to protect the public's health.

CLINICAL SIGNIFICANCE OF ANTIMICROBIAL-RESISTANT *SALMONELLA*

Salmonellosis is an important public health problem in the United States. Although most human *Salmonella* infections result in a self-limiting gastrointestinal illness characterized by diarrhea, fever, and abdominal cramps, infections that spread to the bloodstream, meningeal linings of the brain, or other deep tissue sites, can result in a severe illness leading to disability or death. Each year, an estimated 1.4 million human *Salmonella* infections occur in the United States, causing an estimated 80,000-160,000 persons to seek medical attention, resulting in 16,000 hospitalizations, and nearly 600 deaths.[30] Antimicrobial agents are not essential for the treatment of most *Salmonella* infections,[13.44] but are commonly prescribed for persons who seek medical attention. In surveys conducted by the Centers for Disease Control (CDC) in 1990[17] and 1995, 40% of persons with *Salmonella* infections who sought medical attention were treated with antimicrobial agents, suggesting that 32,000-64,000 persons with *Salmonella* infections are treated with antimicrobial agents each year. Ciprofloxacin, a fluoroquinolone antimicrobial agent, was the most commonly prescribed antimicrobial agent for *Salmonella* infections. Ciprofloxacin, which became available for oral use in humans in the United States in 1988, was used by approximately 25% of persons who received antimicrobial agents in the 1990 survey and 33% in the 1995 survey, suggesting that > 100,000 persons with *Salmonella* infections have been treated with ciprofloxacin in the past 10 years in the United States. The overall usage of ciprofloxacin in human is vast. According to national pharmacy data, ciprofloxacin usage in the United States has remained relatively constant since 1989; 2-3 million persons, including approximately 300,000 persons with acute diarrhea, received ciprofloxacin each year .[10]

In contrast to patients with uncomplicated gastroenteritis, effective antimicrobial agents are essential for the treatment of patients with bacteremia, meningitis, or other extraintestinal *Salmonella* infections. [13.44] In approximately 6% of the culture-confirmed cases reported to CDC, *Salmonella*e are isolated from specimens collected from extraintestinal sites, usually from blood.[9.17] Since approximately 40,000 culture-confirmed cases are reported to CDC each year, effective antimicrobial agents are critical and may be life-saving for at least 2,400 persons a year. The selection of antimicrobial agents for the treatment of invasive infections has become increasingly restricted due to increasing antimicrobial resistance among *Salmonella* isolates. In the past ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole have been the "treatment of choice" for *Salmonella* infections.[26.29.35] However, among 1,272 randomly selected *Salmonella* isolates from humans tested at CDC in the National Antimicrobial Resistance Monitoring System in 1996, 21% were resistant to ampicillin, 10% to chloramphenicol, and 4% to trimethoprim-sulfamethoxazole.[6] In contrast, almost all of the *Salmonella* isolates tested at CDC have been susceptible to fluoroquinolones and third-generation cephalosporins.[6.20.21] For this reason, and because of clinical response and favorable pharn1acodynamic properties, fluoroquinolones and third-generation cephalosporins are the current drugs-of-choice for the treatment of invasive *Salmonella* infections in adults and children, respectively. Should *Salmonella* develop antimicrobial resistance to these two antimicrobial agents, suitable alternative antimicrobial agents are not currently available and serious adverse human health consequences are expected.

Surveys conducted by CDC within selected counties in the United States in 1985,[29]1990,[9] and 1995 of persons with *Salmonella* infection provide data concerning antimicrobial use. Ampicillin use declined from 60% in 1985 to 5% in 1995, whereas the proportion of isolates resistant to ampicillin steadily increased (CDC, unpublished data). Trimethoprim-sulfamethoxazole use, in contrast, remained constant whereas trimethoprim-sulfamethoxazole resistance increased slightly. Importantly, the

proportion of patients with salmonellosis treated with ciprofloxacin or extended-spectrum cephalosporins markedly increased without an emergence of resistance to either of these antimicrobial agents among human *Salmonella* isolates. The continued susceptibility of human *Salmonella* isolates to fluoroquinolones and extended-spectrum cephalosporins was confirmed in more than 4,000 isolates in 199520.21 and 1,200 isolates in 1996.[6]

These data suggest there is little correlation between the antimicrobial agents used in persons with *Salmonella* infections and development of antimicrobial resistance among human *Salmonella* isolates. If human antimicrobial use is not associated with the increasing antimicrobial resistance seen among *Salmonella* isolates, what is causing the increasing prevalence of antimicrobial-resistance observed among *Salmonella* isolates? Before addressing this question, it is useful to review the epidemiology of antimicrobial-resistant pathogens.

EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANT PATHOGENS, INCLUDING *SALMONELLA*

Antimicrobial agents are used: (1) to treat microbial infections in humans, plants, and animals; (2) prophylactically in healthy humans, plants, and animals; and (3) subtherapeutically in food animals to improve their growth rate and feed conversion. There is evidence that the use of antimicrobial agents at subtherapeutic or therapeutic concentrations provides a selective pressure that results in an increase in the prevalence of antimicrobial resistance. However, for an antimicrobial-resistant pathogen to have a public health consequence, there must both usage of the antimicrobial agent that leads to resistance in a pathogen and subsequent transmission of the resistant pathogen. The importance of both use and subsequent transmission can be illustrated by observing the consequences of using fluoroquinolones for the treatment of three different infections: methicillin-resistant Staphylococcus aureus (MRSA) in humans, *Salmonella* in humans, and *Salmonella* in food animals.

The emergence of human MRSA infections in hospitals in the United States is a major public health concern.[32] S. aureus, often spread person-to-person in hospital settings, has become resistant to a number of antimicrobial agents, including methicillin. Ciprofloxacin, the first fluoroquinolone approved in the United States for human use and highly effective against MRSA, became widely used for the treatment of human MRSA infections and showed promise in lessening their public health impact. However, human infections with ciprofloxacin-resistant MRSA rapidly emerged in the United States; by 1991-1992, 85% of MRSA isolates from hospitals in the National Nosocomial Infection Surveillance System were resistant to ciprofloxacin.[14] The rapid emergence of ciprofloxacin-resistance MRSA is clearly related to both the increased use of ciprofloxacin in humans and the efficiency of person-to-person transmission of ciprofloxacin-resistant MRSA in hospitals.

As indicated earlier, ciprofloxacin has also been widely used for the treatment of *Salmonella* infections in humans. Because antimicrobial resistance follows antimicrobial usage, *Salmonella* with decreased susceptibility to ciprofloxacin may have developed in persons with salmonellosis who were treated with ciprofloxacin. However, person-to-person transmission of *Salmonella* is relatively rare in the developed world so such strains have not had the opportunity to disseminate in the United States.
This is in direct contrast to the situation in the United Kingdom. In 1993, a

fluoroquinolone (enrofloxacin) was licensed for use in food animals and human *Salmonella* isolates with decreased susceptibility to ciprofloxacin were rare. Following the approval of enrofloxacin for veterinary use, decreased susceptibility to fluoroquinolones (MIC ~ 0.25) rapidly emerged among human *Salmonella* isolates, particularly among isolates of *Salmonella* serotype Typhimurium DT104, that were resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (R-type ACSSuT). DT014 R-type ACSSuT has emerged as the second most common strain of *Salmonella* isolated from humans. In 1993, none of the DT104 R-type ACSSuT isolates had a decreased susceptibility to fluoroquinolones; by 1996, 14% had a decreased susceptibility. [42] A parallel rapid emergence of decreased susceptibility to fluoroquinolones, as indicated by antimicrobial resistance to nalidixic acid, has been observed among animal *Salmonella* Typhimurium DT 104 T -type ACSSuT isolates at the central veterinary diagnostic laboratory in the United Kingdom.

SOURCES OF *Salmonella* INFECTIONS

Salmonella lives in the intestines of mammals, birds, and reptiles. Once shed into the environment in the feces of infected animals, *Salmonella* may survive for long periods in water, soil, and on or within foods. In less developed countries, person-to person transmission may account for a significant proportion of human *Salmonella* infections and nosocomial sources of antimicrobial-resistant *Salmonella* have been identified. [11] Before the development of hospital infection control procedures in the United States, nosocomial outbreaks of salmonellosis due to person-to-person transmission, particularly in newborn nurseries, were not infrequent.[40]

In contrast, most human *Salmonella* infections in the United States occur from the ingestion of contaminated food, and many of these foods are of animal origin. Direct fecal-oral transmission following contact with animal feces is another, less common, source of human salmonellosis. At least six lines of evidence can be presented which taken together, demonstrate that foods of animal origin are the dominant source of human salmonellosis, and suggest that person-to-person transmission is an uncommon source of human salmonellosis in the United States.

Carriage rates in reservoir species

Although the prevalence varies, *Salmonella* is frequently isolated from the feces of food animals, companion animals, and wild animals. In longitudinal studies, some animals may excrete *Salmonella* for long periods of time. For example, many birds, including poultry , are infected with *Salmonella* and shed the organism in their feces (an estimated 20% of retail pack ages of poultry are contaminated with *Salmonella*). Fecal excretion of *Salmonella* by humans, in contrast, is relatively uncommon among apparently healthy individuals and is fairly short-lived among persons with salmonellosis. A review of several surveys of stool specimens from apparently healthy persons found a median carriage rate of *Salmonella* of 0.15%.5 A review of several outbreak investigations determined the median duration of excretion by persons with salmonellosis to be about 4 weeks.[10]

Infectious dose

Volunteer studies among healthy adults suggest that, although a small oral dose of *Salmonella* given in water may be sufficient to infect a small proportion of recipients, a large dose (~ 106 organisms) usually is necessary to cause infection in a high proportion of recipients.[28] In contrast; pathogens with low infectious doses (e.g.,

Shigella and Escherichia coli O 157) commonly spread person-to-person in such settings. Furthermore, the relative low frequency of secondary illness within households in which a primary culture-confirmed case is identified and the great rarity of day-care center outbreaks of salmonellosis suggests that person-to-person transmission of *Salmonella* occurs infrequently.

Outbreak investigations

Although outbreaks only represent a fraction of the cases of *Salmonella* infections that occur, much insight into the epidemiology of salmonellosis has been provided through investigations of outbreaks. Most outbreak investigations are conducted by state or local health departments who report foodborne disease outbreaks to CDC as part of the Foodborne Disease Outbreak Surveillance System.[4] A small number of investigations are conducted each year by CDC in collaboration with state and local health departments.

Between 1988 and 1992, an average of 110 outbreaks of *Salmonella* were reported each year to CDC.4 Sixty percent of these outbreaks were caused by *Salmonella* serotype Enteritidis and most of these were attributed to eating undercooked eggs. These egg-associated outbreaks were often traced back to their farm of origin and it was demonstrated repeatedly that infected hens were the source of the outbreak.[I] Among outbreaks caused by *Salmonella* serotypes other than Enteritidis, a variety of food items were implicated particularly other foods of animal origin. A few of these outbreaks were traced back to their farm of origin. Although some outbreaks involved infected food handlers and food handler illness preceded the outbreak, this was not the typical scenario. In most cases, the food handlers also ate the contaminated foods. Taken together, outbreak investigations demonstrate that foods, particularly foods of animal origin, are the most important source of *Salmonella* infections in humans.

Case-control studies of sporadic infections

Investigations of persons with sporadic *Salmonella* infections (infections that were not recognized to be associated with an outbreak) provide further evidence that foods of animal origin are associated with many human *Salmonella* infections. However, few such investigations have been reported, perhaps because investigations of sporadic infections are less likely to implicate a common source.

Case-control studies of sporadic cases of *Salmonella* Enteritidis were conducted in New York in 1989,[31] California in 1994,[33] and Utah in 1995.[7] These studies each demonstrated that eating raw or undercooked eggs was the most importan1 risk factor for acquiring infections. Several case-control studies of sporadic *Salmonella* cases involving serotypes other than Enteritidis have been reported. Investigations of infections caused by a variety of serotypes in Switzerland[36] (1996) and California[25] (1984) implicated eggs and poultry, respectively, as the most important sources of infections. A study of *Salmonella* Dublin infections in California (1985) implicated raw milk consumption[34] and studies of *Salmonella* Typhimurium and Enteritidis infections in Minnesota (1989 and 1990) identified eggs as the most important source for both infections.[18]

Molecular "fingerprinting"

After identification of the particular *Salmonella* serotype, several subtyping methods (e.g., phage typing, pulsed-field gel electrophoresis, plasmid profiling, ribotyping) may be used to differentiate *Salmonella* isolates further.[41] Such subtyping techniques may be useful in epidemiological investigations to support or refute the postulated source of

the outbreak. For example, in the 18 outbreaks of *Salmonella* Enteritidis in 1990 and 1991 in which eggs were implicated as the source, traceback and environmental investigations on the implicated farms detected the human outbreak strain of *Salmonella* Enteritidis, as determined by phage type, from the environment (100%) and from internal organs (88%) of implicated flocks, strongly suggesting that the implicated farms were the sources of the outbreaks.[l] In Denmark, phage-typing and plasmid profiling of *Salmonella* Typhimurium isolates from human and animal sources showed some animal strains and human strains to be indistinguishable; the spread of the strains from animals to humans was the most probable explanation for this phenomenon.[37]

Emergence of unusual strains in humans

Monitoring of human *Salmonella* surveillance data, when supported by serotyping and perhaps additional subtyping techniques, can enable detection of the emergence of unusual strains of *Salmonella*. Possible sources for an increased number of an unusual strain of *Salmonella* among human isolates may be indicated by the emergence of the same unusual strain among isolates from animals, foods, and other sources. Such investigations often reveal the source of the increase has been traced to foods of animal origin. For example, beginning in 1969 there was a marked increase in human isolates of *Salmonella* Agona detected in the United States and several other countries. *Salmonella* Agona had not been isolated in the United States before 1969, but by 1972 it was the eighth most common serotype isolated from humans in the United States.[12] Field investigations and surveillance data determined Peruvian fish meal fed to chicken was the source of the infections. The identification of *Salmonella* Agona from Peruvian fish meal in routine surveillance sampling of fish meal in 1970 was critical in identifying this new vehicle.

The widespread geographic distribution of unusual strains also supports a limited role for person-to-person transmission of *Salmonella* in the developed world. For example, the widespread emergence in the United States and Europe of *Salmonella* Agona, and more recently an indistinguishable clone of multidrug-resistant *Salmonella* Typhimurium DT104 R-type ACSSuT ,[16] suggests transmission via the contamination of a widely distributed vehicle such as food, rather than infected persons.

Although comparisons between human and animal *Salmonella* surveillance data are useful in investigating the epidemiology of salmonellosis, such comparison should consider the specimen collection practices inherent in the submission of specimens to clinical laboratories within each surveillance system. For example, for both human and animal isolates, the specimens submitted to the clinical laboratories usually are collected from ill individuals. Because the serotypes of *Salmonella* in ill animals and in foods of animal origin, which come from apparently healthy animals, are likely to be different, crude comparisons of the "top ten" *Salmonella* serotypes in humans and in animals can lead to the erroneous conclusion that *Salmonella* serotypes that are common in certain animals (e.g., *Salmonella* serotype Cholerasuis in swine) and rare in humans are nonpathogenic to humans. Thus, comparisons of the most common serotypes in certain animals and humans cannot be used to conclude that food animals are not the most common sources of certain serotypes.

SOURCES OF ANTIMICROBIAL-RESISTANT *SALMONELLA* INFECTIONS IN HUMANS

Most human *Salmonella* infections in the United States are acquired from ingestion of

contaminated foods; therefore, the majority of antimicrobial-resistant *Salmonella* infections are acquired from ingestion of foods contaminated with antimicrobial-resistant *Salmonella*. Another, less common, source of antimicrobial-resistant *Salmonella* is direct fecal--oral transmission following contact with animal feces. Given the number of human *Salmonella* infections per year and that contaminated foods are the primary vehicle, the factors concerning the emergence and increasing prevalence of antimicrobial-resistant *Salmonella* are of public health importance.

The emergence and increasing prevalence of antimicrobial-resistant *Salmonella* is related to antimicrobial usage. In the United States, antimicrobial agents are primarily used in humans, animals, and on plants. Human antimicrobial usage in the United States has limited impact on resistance among *Salmonella* and most persons infected with antimicrobial-resistant *Salmonella* do not have a history of recent international travel.[9,29,35] Few antimicrobial agents are used on plants; therefore, the likely cause for the emergence and increasing prevalence of antimicrobial-resistant *Salmonella* in the United States is the use of antimicrobial agents in animals, predominately food animals. Four lines of evidence support the conclusion that antimicrobial-resistance among *Salmonella* isolates in humans results from the use of antimicrobial agents in food animals.

Tracebacks of selected foodbome disease outbreaks

Several outbreak investigations of antimicrobial-resistant *Salmonella* infections in humans have combined epidemiologic fieldwork and laboratory subtyping techniques to trace antimicrobial-resistant *Salmonella* through the food distribution system to farms and antimicrobial use on the farms was found to be associated with the antimicrobial resistance. [16,22,27,38,39] One investigation, using a unique plasmid profile, traced hamburgers contaminated with antimicrobial-resistant *Salmonella* from supermarkets through meat processing to well beef cattle that had been feed antimicrobial agents.[22] Another investigation of approximately 1,000 persons infected with antimicrobial-resistant *Salmonella* serotype Newport used an unusual marker -- chloramphenicol resistance. Chloramphenicol-resistant *Salmonella* Newport was traced from ill persons through processing of contaminated hamburger to a dairy farm area. A survey of dairy farms shows a significant association between isolation of chloramphenicol-resistant *Salmonella* from manure lagoons and reported farm use of chloramphenicol.[38] A review of 52 outbreaks of *Salmonella* infections investigated by CDC between 1971 and 1983 demonstrated that outbreaks caused by antimicrobial-resistant *Salmonella* were more likely to have a food animal source than outbreaks caused by antimicrobial-susceptible *Salmonella*.[23]

Emergence of Salmonella Typhimurium DT104 R-type ACSSuT with decreased susceptibility to fluoroquinolones in the United Kingdom

The emergence of *Salmonella* Typhimurium DT 104 with decreased susceptibility to fluoroquinolones in humans in the United Kingdom provides evidence that antimicrobial resistance among *Salmonella* isolates in humans results from the use of antimicrobial agents in food animals. Decreased susceptibility to fluoroquinolones among human *Salmonella* isolates were rare in the United Kingdom prior to 1993, despite the widespread use of ciprofloxacin in humans since 1987. This parallels the current situation in the United States where fluoroquinolone use in humans since 1988 appears to have had no impact on resistance in *Salmonella*. As previously stated, following the 1993 approval and widespread use of enrofloxacin in veterinary medicine in the United Kingdom, human *Salmonella* isolates (and animal isolates) with decreased susceptibility to ciprofloxacin were noted in 1994 and have increased

since.[42]

Comparison of pattems of antimicrobial resistance patterns of Salmonella isolates from humans and animals

If veterinary use of antimicrobial agents is responsible for the development of antimicrobial resistant *Salmonella* in animals, which may be transmitted to humans, the patterns of antimicrobial resistance observed among *Salmonella* isolates collected from healthy animals can be expected to resemble those in humans. These similarities become most evident when focusing on a serotype of *Salmonella* in humans that are predominately derived from a single animal source. For example, human infections with *Salmonella* serotype Heidelberg are often associated with eating undercooked chicken. The antimicrobial resistance patterns of *Salmonella* Heidelberg isolates from humans and healthy chickens are similar.

Comparing patterns of antimicrobial usage in humans and animals with antimicrobial resistance patterns among humans and animals

Although limited data are available on antimicrobial agent usage (subtherapeutic and therapeutic) in food animals, the available data suggest that the patterns of antimicrobial usage in food animals are similar to the spectrum of antimicrobial resistance observed among *Salmonella* isolates from food animals and humans. In contrast, the patterns of antimicrobial agent usage in humans are dissimilar to the spectrum of antimicrobial resistance observed in humans.

HUMAN HEALTH RISKS OF FLUOROQUINOLONE USE IN FOOD ANIMALS

With the knowledge that foods of animal origin are the source of most human *Salmonella* infections (including most antimicrobial-resistant *Salmonella* infections), and that antimicrobial resistance among *Salmonella* isolates in the United States is related to the use of antimicrobial agents in food animals, it is possible to estimate the potential human health consequences of unrestricted veterinary use of fluoroquinolones in the United States using the human health risks model developed by the Institute of Medicine in 1988.[24] Each year in the United States, there are approximately 2,400 persons with life-threatening invasive *Salmonella* infections, most of whom are treated with antimicrobial agents, and many of whom are treated with fluoroquinolones and recover from their infections. Antimicrobial agents, particularly fluoroquinolones, are therefore lifesaving for approximately 2000 persons a year. Few persons have had fluoroquinolone-resistant *Salmonella* infections; therefore, the clinical significance of fluoroquinolone-resistance is not precisely known. However, because other antimicrobial treatment options are limited, treatment failures and serious outcomes, including deaths, would be expected. Assuming 10% of *Salmonella* isolates in the United States were to become fluoroquinolone-resistant and 5% of persons with invasive fluoroquinolone-resistant infections were to die (who would otherwise have survived if the infection was fluoroquinolone-susceptible), the result would be an increase of 10 deaths per year. If 50% of strains were resistant, there would be 100 additional deaths a year.

NEED FOR PRUDENT USE OF ANTIMICROBIAL AGENTS IN FOOD ANIMALS

The emergence and increasing prevalence of antimicrobial-resistant *Salmonella* complicates the treatment of *Salmonella* infections in humans and animals. The increasing prevalence of antimicrobial resistance among *Salmonella* isolates and other pathogens, specifically the potential emergence of fluoroquinolone-resistant infections with adverse human health consequences, means that additional measures are needed to reduce the emergence and dissemination of resistant pathogens. Measures should include implementation of strategies of controlling the spread of pathogens on the farm such as improved hygiene and sanitation, feed safety, and the use of probiotics. Such efforts to minimize dissemination of antimicrobial-resistant pathogens should be emphasized.[19] Steps should also be taken to ensure that antimicrobial agents are used prudently in food animals. As proposed in human medicine, prudent usage of antimicrobial agents maximizes the therapeutic effect of the antimicrobial agent and minimizes the development of antimicrobial resistance. Potential components of prudent use strategies include defining the need for the treatment and ensuring the appropriate therapeutic doses and regimens.

Subtherapeutic (growth promotion) uses of antimicrobial agents represent a separate category of use, because these agents are not given to their therapeutic effect and may be replaced by non-antimicrobial methods of growth promotion. The potential economic benefit of subtherapeutic uses should be weighed against the cost of the resistance they may promote in both animal and human foodborne pathogens. It is difficult to justify such uses as prudent. Because the subtherapeutic use of penicillin and tetracyclines most likely contributes to the development and dissemination of antimicrobial resistant *Salmonella*, such as multidrug-resistant *Salmonella* Typhimurium DTI04, the subtherapeutic use of these antimicrobials should be reconsidered in particular .[45]

Fluoroquinolones are a vital class of antimicrobial agents for the treatment of potentially life-threatening *Salmonella* infections in humans. Widespread usage of fluoroquinolones in food animals will lead to rapid emergence and dissemination of resistant infections to humans. Because of the adverse human health consequences of these infections, the use of fluoroquinolones in food animals should be restricted until validated guidelines for the prudent use of antimicrobial agents in food animals have been implemented and certified and adequate public health safeguards have been established to minimize the development and dissemination of antimicrobial resistance and dissemination of *Salmonella* resistant to these agents.

REFERENCES

1. **Altekruse, S., J. Koehler, F. Hickman-Brener, R.V. Tauxe, and K. Ferris**. 1993. A comparison of *Salmonella* enteritidis phage types from egg-associated outbreaks and implicated laying flocks. Epidemiol. Infect. 110:17-22.
2. **Anonymous**: 1994. FDA panel urges restricted use of fluoroquinolones in animals. ASM News 60:350-351.
3. **Beam, Jr. T .R.** 1994. Fluoroquinolones in animal feeds. ASM News 60:348-349.
4. **Bean, N.H., J.S. Goulding, C. Lao, and F.J. Angulo**. 1996. Surveillance for Foodborne Disease Ourbreaks-United States, 1988-1992. Morbidity and Mortality Weekly Report Surveillance Summary 45(SS-5: 1-65.
5. **Buchwald, D.S., and M J. Blaser**. 1984. A review of human salmonellosis: II. Durations of excretion following infection with non typhi *Salmonella*. Rev. Infect. Dis. 6:345-356.

6. **Centers for Disegse Control and Prevention**. 1996. CDC/FDA/USDA National Antimicrobial Monitoring System 1996 Annual Report. Atlanta, GA.
7. **Centers for Disease Control and Prevention**. 1996. EPI-AID 96-16, Trip report: investigation of increased incidence of *Salmonella* Enteritidis isolates in Utah. July, 1996.
8. **Centers for Disease Control and Prevention**. 1996. Establishment of a national surveillance program for antimicrobial resistance in *Salmonella*. Morbidity and Mortality Weekly 45:110-111.
9. **Centers for Disease Control and Prevention**. 1996. *Salmonella* Surveillance, Atlanta, GA.
10. **Chalker, R.B., and M.J. Blaser**. 1988. A review of human salmonellosis: III. Magnitude of *Salmonella* infection in the United States. Rev. Infect. Dis.10:111-124.
11. **Chembin, C.E**. 1981. Antibiotic resistance of *Salmonella* in Europe and the United States. Rev. Infect. Dis. 3:1105-1126.
12. **Clark, G.M., A.F. Kaufmann, and E.J. Gangrosa**. 1973. Epidemiology of an international outbreak of *Salmonella* agona. Lancet 1973,490-493.
13. **Conte, I.E.** 1995. Manual of antibiotics and infectious diseases. Williams & Wilkins, Baltimore.
14. **Coronado, V .G., Edwards, I.R., Culver, D.H., and R.P. Gaynes**. 1995. Ciprofloxacin resistance among nosocomial Pseudomonas aeruginosa and Staphylococcus aureus in the United States. National Nosocomial Infections Surveillance (NNIS) System. Infect. Control Hosp. Epidemiol. 16:71 75.
15. **Federal Register**. May 22, 1997.62(99):27944-27947.
16. **Glynn, M.K., C. Bopp, W. Dewitt, P. Dabney, M. Mokhtar, and F. Angulo**. 1998. Recent emergence of multidrug resistant *Salmonella* enterica serotype Typhimurium DT104 infections in the United States. N. Engl. I. Med. 339:1333-1338.
17. **Hargrett-Bean, N.T., A.T. Pavia, and R.V. Tauxe**. 1988. *Salmonella* isolates from humans in the United States, 1984-1986. Morbidity and Mortality Weekly Report Surveillance Summary 37(SS-2):25-31.
18. **Hedberg, C.W., M.J. David, K.E. White, K.L. MacDonald, and M. T. Osterholn**. 1993. Role of egg consumption in sporadic *Salmonella* enteritidis and *Salmonella* typhimurium infections in Minnesota. I. Infect. Dis. 167:107-111.
19. **Helmuth, R., and D. Protz**. 1997. How to modify conditions limiting resistance in bacteria in animals and other reservoirs. Clin. Infect. Dis. 24(Suppl. 1): 136-138.
20. **Herikstad, H., P.S. Hayes, I. Hopn, P. Floyd, L. Snyder, and F. Angulo**. 1997. Ceftriaxone-resistant *Salmonella* in the United States. Pediatr. Infect. Dis. I. 16:904-905.
21. **Herikstad, H., P. Hayes, M. Mokhtar, M.L. Fracaro, EJ . Threlfall, and F. Angulo**. 1997. Emerging quinolone-resistant *Salmonella* in the United States. Emerging Infect. Dis. 3:371-372.
22. **Holmberg, S.D., M. T. Osterholm, K.A. Senger, and M.L. Cohen**. 1984. Drug-resistant *Salmonella* from animals fed antimicrobials. N. Engl. I. Med. 311:617-622.
23. **Holmberg, S.D., I.G. Wells, and M.L. Cohen**. 1984. Animal-toman transmission of antimicrobial-resistant *Salmonella*: investigations of U.S. outbreaks 1971-1983. Science 225:833-835.

24. **Institute of Medicine**. 1989. Human health risks with subtherapeutic use of penicillin or tetracycline in animal feed. National Academy Press, Washington, DC.
25. **Kass, P.H., T.B. Farver, IJ. Beaumont, C. Genigeorgis, and F. Stevens**. 1992. Disease determinants of sporadic salmonellosis in four northern California counties: a case-control study of older children and adults. Ann. Epidemiol. 2:683-696.
26. **Lee, LA., N.D. Puhr, K. Maloney, N.H. Bean and R. V. Tauxe**. 1994. Increase in antimicrobial-resistant *Salmonella* infections in the United States, 1989-1990. J. Infect. Dis. 170:128-134.
27. **Lyons, R. W ., C.L. Samples, H.N. DeSilva, K.A. Ross, E.M. Julian, and PJ. Checko**. 1980. An epidemic of resistant *Salmonella* in a nursery: animal-to-human spread. J. Am.. Med. Assn. 243:546-547.
28. **McCullough, N.B., and C.W. Eisele**. 1951. Experimental human salmonellosis: I. Pathogenicity of strains ot *Salmonella* meleagridis and *Salmonella* anatum obtained from spray-dried whole egg. I. Infect. Dis. 88:278-289.
29. **McDonald, K.L., M.L. Cohen, N. Hargrett-Bean, I.G. Wells, N.D. Puhr, S.F. Collin, and P.A. Blake**. 1987. Changes in antimicrobial resistance of *Salmonella* isolated from humans in the United States. I. Am. Med. Assn. 258: 1496-1499.
30. **Mead, P..S., L. Slutsker, V. Dietz, L.F. McCaig, J.S. Bresee, C. Shapiro, P. Grifrm, and R.V. Tauxe**. 1999. Food-related illness and death in the United States. Emerging Infect. Dis. 5:607-625.
31. **Morse, D.L., G.S. Birkhead, I. Guardino, S.F. Kondracki, and J.J. Guzewich**. 1994. Outbreak and sporadic egg-associated cases of *Salmonella* enteritidis: New York experience. Am. I. Public Health 84:859-860.
32. **Panlilio A.L., D.H. Culver, R. Gaynes, J.S. Tolson, and W .J. Martone**. 1992. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975-1991. Infection Control Hosp. Epidemiol. 13:582-586.
33. **Passaro, D.J., R. Reporter, L. Mascola, L. Kilman, G.B. Malcolm, J. Rolka, S.B. Werner, and DJ. Vulia**. 1996., Epidemic *Salmonella enteritidis* infection in Los Angeles County, California the predominance of phage type 4. Western 1. Med. 165: 126-130.
34. **Richwald, G.A., S. Greenland, B.J. Johnson, J.M. Friedland, E.J.C. Goldstein and D.T. Plichta**. 1988. Assessment of the excess risk of *Salmonella* dublin infection associated with the use of certified raw milk. Public Health Rep. 103:489-493.
35. **Riley, L. W., M.L. Cohen, J.E. Seals, M.J. Blaser, K.A. Birkness, N.T. Hargrett, S.M. Martin, and R.A. Feldman**. 1984. Importance of host factors in human salmonellosis caused by multiresistant strains of *Salmonella*. J. Infect. Dis. 149:818-883.
36. **Schmind, H., A.P .Burnens, A. Baumgartner, and J. Oberreich. 1996. Risk factors for sporadic salmonellosis in Switzerland**. Eur .J. Clin. Microbiol. Infect. Dis. 15:725-732.,
37. **Seyfarth, A.M., B.C. Wegner, and N. Frimodt-Moeller**. 1997. Antimicrobial resistance in *salmonella enterica* subsp. enterica serovar typhimurium from humans and production animals. I. Antimicrob. Chemother. 40:67-75.
38. **Spika, J.S., S.H. Waterman, G.W. Soo Hoo, M.E. St. Louis, R.E. Pacer, S.M. James, M.L. Bissett, L.W. Mayer, J.Y. Chiu, B. Hall, K. Greene, M.E. Potter, M.L. Cohen, and P.A. Blake**. 1987. Chloramphenicol-resistant

salmonella newport traced through hamburger to dairy farms. N. Engl. J. Med. 316:565-570.

39. **Tacket, C.O., L.B. Dominguez, H.J. Fisher, and M.L. Coben**. 1985. An outbreak of multiple-resistant *Salmonella enteritis* from raw milk. J. Am. Med. Assn. 253:2058-2060.
40. Tauxe, R.V.. 1986. Antimicrobial resistance in human salmonellosis in the United States. J. Animal Sci. 62 (Suppl. 3):65-73.
41. **Threlfall, E.J., N.G. Powel, and B. Rowe**. 1994. Differentiation of *salmonella*s by molecular methods. PHLS Microbiol. Dig. 11:199-202.
42. **Threlfall, E.J., L.R. Ward, and B. Rowe**. 1997. Increasing incidence of resistance to trimethoprim and ciprofloxacin in epidemic *salmonella Typhimurium* DT104 in England and Wales. Eurosurveillance 2:81-84.
43. **U.S. Congress, Office of Technology Assessment.** Impacts of antibiotic-resistant bacteria. Washington, DC: U.S. Government Printing Office; 1995 [OTA-H-629].
44. **Wilcox, M.B., and R.C. Spencer.** 1992. Quinolones and *salmonella* gastroenteritis. J. Antimicrob. Chemother.30:221-228.
45. **World Health Organization, Division of Emerging and other Communicable Diseases Surveillance and Control**. The medical impact of the use of antimicrobials in food animals. Geneva, World Health Organization 1997;WHO/EMC/ZOO/97.4:1-12.

Suggested citation:

Angulo F, Johnson K, Tauxe R, Cohen M. Significance and sources of antimicrobial-resistant nontyphoidal *Salmonella* infections in the United States. Microbial Drug Resistance 2000; 6 (1): 77-83.